



TITLE:

# A Case of Noonan Syndrome with Multiple Subcutaneous Tumours with MAPK-ERK/p38 Activation

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## SHORT COMMUNICATION

### A Case of Noonan Syndrome with Multiple Subcutaneous Tumours with MAPK-ERK/p38 Activation

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Noonan syndrome (NS) is an autosomal dominant disorder with a frequency of 1/1,000 to 1/2,500 live births (1, 2). The symptoms of NS include short stature, specific facial features such as hypertelorism and posteriorly rotated ears, epicanthal folds, congenital heart failure, and webbed neck. Although skin tumours are not common features in patients with NS, several cases of NS with multiple granular cell tumours in the skin have been reported (3).

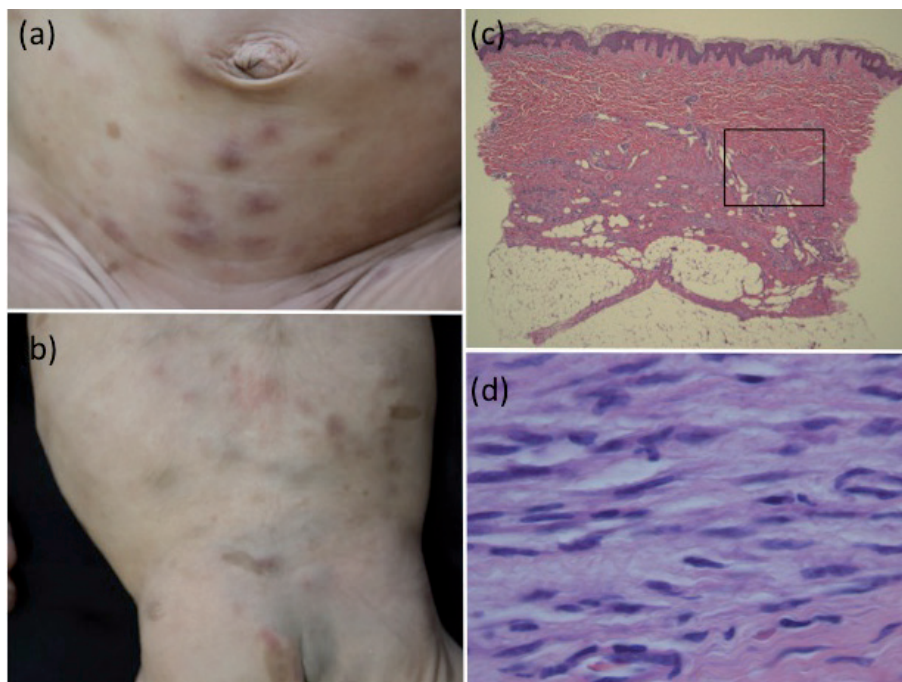
Thus far, heterozygous mutations in 9 genes have been documented to underlie this disorder, and approximately 75% of patients clinically diagnosed with NS harbour a mutation in those genes (2). It has been revealed that the genes involved in NS are regulators of rat sarcoma viral oncogene (RAS)-mitogen-activated protein kinase (MAPK) pathways, especially the RAS-ERK pathway, which plays a crucial role in various physiological processes, such as cell proliferation, survival and differentiation (4). Since gene mutations in NS are gain-of-function mutations, it has been suggested that activation of the RAS-MAPK signalling pathway might be involved in the development of NS. However, whether and how such activation is involved in the clinical symptoms of NS remains unclear. We report

here a case of NS with atypical multiple subcutaneous tumours with RAS-MAPK activation.

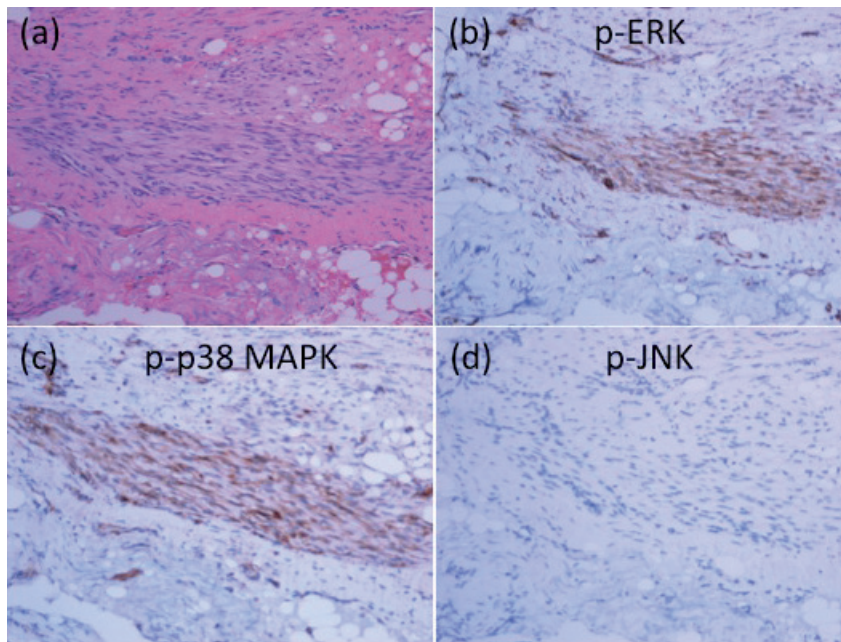
## CASE REPORTS

A 2-year-old girl diagnosed with NS was referred to our dermatology department for evaluation of multiple skin nodules on her trunk. The patient had been clinically diagnosed with NS based on congenital heart failure and several congenital anomalies, such as webbed neck and epicanthal folds. Cutaneous nodules were detected at birth, and their number and size had increased gradually with age. On examination, the patient exhibited multiple skin-coloured nodules on her lower abdomen (Fig. 1a). Some café-au-lait spot-like pigmented macules were also detected on her abdomen and back (Fig. 1a and b). Histological analysis of the nodules revealed hyperplasia of fibroblast-like spindle cells in the lower dermis (Fig. 1c and d). No granular cell tumour-like cells, which have a granular appearance in the cytoplasm, were observed. To characterize the nature of the tumour cells in more detail, immunohistochemical analysis was performed using anti-smooth muscle actin, S-100, desmin,  $\beta$ -catenin, CD68, factor XIIIa, and CD34 antibodies. However, no positive signals were detected in the tumours with the above antibodies (data not shown), suggesting that the tumour cells are mesenchymal in origin and composed mainly of fibroblasts.

To investigate whether activation of the RAS-MAPK signalling pathway was involved in the tumour formation, further immunohistochemical analysis of the tumour was performed.



**Fig. 1.** Clinical symptoms and histology of subcutaneous tumours. (a) Multiple subcutaneous tumours on the lower abdomen. (b) Café-au-lait spot-like pigmented macules on the back. (c) Low magnification view (4 $\times$ ) of haematoxylin and eosin-stained section. Fibrous structures are detected in the lower dermis and fat tissues. The square indicates the region selected for high-magnification view. (d) High-magnification view (100 $\times$ ) in (c). Hyperplasia of fibroblast-like spindle cells is detected among the collagen fibres. Written consent to publish was obtained from the patient.



*Fig. 2.* Immunohistochemical analysis for various mitogen-activated protein kinase (MAPK) in the subcutaneous tumour cells. (a) Haematoxylin and eosin (HE) staining for the subcutaneous tumours. Immunohistochemical analysis for (b) phosphorylated extracellular signal-regulated kinase (p-ERK), (c) phosphorylated p38 MAPK (p-p38 MAPK), and (d) phosphorylated c-Jun N-terminal kinase (p-JNK). Brown signals indicate positive signals for each antibody. Original magnification 40 $\times$ .

Phosphorylation of 3 MAPK, i.e. extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, was examined. Positive signals for phosphorylated (p)-ERK and p-p38 MAPK were clearly detected in the cytoplasm of tumour cells (Fig. 2 a–c), indicating that both ERK and p38 MAPK are activated in the tumour cells. On the other hand, no positive signals for p-JNK were detected (Fig. 2d).

## DISCUSSION

NS is one of the syndromes called neuro-cardio-facial-cutaneous syndromes (NCFC), which include several disorders, such as Noonan, neurofibromatosis type 1 (NF1), LEOPARD, Costello and cardiofaciocutaneous syndrome (1). Germline mutations in genes coding for different components of the RAS-MAPK signalling have been recognized as the cause of NCFC (1). It has been reported that NCFC sometimes develop multiple subcutaneous tumours, such as neurofibroma in NF1 (1, 2) and granular cell tumours in NS (3), but histological characteristics of the tumours in the current case did not correspond to those of such tumours. In addition, desmoid tumours (5), dermatofibroma, and dermatofibrosarcoma protuberans were other possible differential diagnoses, but the results obtained from the immunohistochemical analysis did not support such diagnoses. Taken together, the tumour cells seem to be of mesenchymal origin and composed mainly of fibroblasts. As far as we have examined, we were not able to find similar NS cases that manifest fibroblastic tumours as observed in the current case. In addition, the patient exhibited café-au-lait spot-like pigmented macules, which is also an atypical feature in NS (1, 2).

The gene mutations in NS are gain-of-function mutations; therefore, various clinical symptoms in NS,

including skin tumours, may be caused by aberrant activation of the RAS-MAPK pathway (1, 2). However, direct evidence of the association between RAS-MAPK activation and the clinical symptoms of NS remains unclear. In the case reported here we clearly observed ERK activation in the tumours, which may provide evidence of the involvement of RAS-MAPK activation for clinical symptoms in NS. In addition to ERK, p38 MAPK activation was observed in the present case. Because all known gene mutations in NS are regulators of the RAS-ERK pathway (1, 2) but not the p38 MAPK pathway, our patient may have some new or additional mutations in unknown molecules other than ERK pathway, which might lead to the development of the multiple subcutaneous tumors with ERK/p38 activation.

*The authors declare no conflicts of interest.*

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